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Markers of central inflammation in major depressive disorder: a systematic review and meta-analysis of studies examining cerebrospinal fluid , positron emission tomography and post-mortem brain tissue.

Daniela Enache[a,b]: The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, London, SE5 9RT, daniela.enache@ki.se

Carmine Pariante[a,c]: The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, London, SE5 9RT: carmine.pariante@kcl.ac.uk

Valeria Mondelli[a,c]: The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, London, SE5 9RT: valeria.mondelli@kcl.ac.uk

[a] King's College London, Institute of Psychiatry, Psychology and Neuroscience, Department of Psychological Medicine, London, UK

[b] Department of Neurobiology, Care Sciences and Society, Division of Neurogeriatrics, Karolinska Institutet, Stockholm, Sweden

[c] National Institute for Health Research Mental Health Biomedical Research Centre, South London and Maudsley NHS Foundation Trust and King's College London, London, UK.

Corresponding author:

Dr Valeria Mondelli

The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, London, SE5 9RT, UK

Email address: valeria.mondelli@kcl.ac.uk

Abstract

Background: Increased peripheral inflammation has been consistently reported in patients with major depressive disorder (MDD). However, only few studies have explored markers of central (brain) inflammation in patients with MDD.

The aim of this study is to systematically review in vivo and post-mortem markers of central inflammation, including studies examining cerebrospinal fluid (CSF), positron emission tomography, and post-mortem brain tissues in subjects suffering with MDD compared with controls.

Methods: PubMed and Medline databases were searched up to December 2018. We included studies measuring cerebrospinal fluid (CSF) cytokines and chemokines, positron emission tomography (PET) studies; and post-mortem studies measuring cytokines, chemokines and cell-specific markers of microglia and astrocytes, all in MDD. A meta-analysis was performed only for CSF and PET studies, as studies on post-mortem markers of inflammation had different cell-specific markers and analysed different brain regions.

Results: A total of 69 studies met the inclusion criteria. CSF levels of IL-6 and TNF-α were higher in patients with MDD compared with controls (standardised mean difference SMD 0.37, 95%CI: 0.17-0.57 and SMD 0.58, 95%CI 0.26-0.90, respectively). CSF levels of IL-6 were increased in suicide attempters regardless of their psychiatric diagnosis. Translocator protein, a PET marker of central inflammation, was elevated in the anterior cingulate cortex and temporal cortex of patients with MDD compared with controls (SMD 0.78, 95%CI: 0.41 - 1.16 and SMD 0.52, 95%CI: 0.19 – 0.85 respectively). Abnormalities in CSF and PET inflammatory markers were not correlated with those in peripheral blood. In post-mortem

studies, two studies found increased markers of microglia in MDD brains, while four studies found no MDD related changes. Of the studies investigating expression of cell-specific marker for astrocytes, thirteen studies reported a decreased expression of astrocytes specific markers, two studies reported increased expression of astrocytes specific markers, and eleven studies did not detect any difference. Four out of six studies reported decreased markers of oligodendrocytes in the prefrontal cortex. Post-mortem brain levels of tumor necrosis alpha (TNF-α) were also found increased in MDD.

Conclusions: Our review suggests the presence of an increase in IL-6 and TNF-alpha levels in CSF and brain parenchyma, in the context of a possible increased microglia activity and reduction of astrocytes and oligodendrocytes markers in MDD. The reduced number of astrocytes may lead to compromised integrity of blood brain barrier with increased monocyte recruitment and infiltration, which is partly supported by post-mortem studies and by PET studies showing an increased TSPO expression in MDD.

Key words: depression; inflammation; cerebrospinal fluid; cytokines; PET microglia; post-mortem glial cells; microglia; astrocytes.

1. Introduction

The role of inflammation in the pathophysiology of major depressive disorder (MDD) is increasingly acknowledged. The evidence derives from both epidemiological studies, which have linked increased peripheral (e.g., blood) inflammation and MDD, and from animal models and human studies showing development of depressive symptoms following administration of immune challenges (Raison et al., 2010). Many studies have now investigated the presence of central inflammation in patients with MDD; however, these studies often focus on different markers of neuroinflammation, making it difficult to interpret inconsistent findings. The presence and the role of immune activation in the brain of patients with MDD remain, therefore, still partly unclear.

In this review of central inflammation in MDD, we focus on different markers of immune dysregulation in the brain, including levels of cytokines in the cerebrospinal fluid (CSF) and measures of number and function of brain cells involved in immune regulation, such as microglia, astrocytes and oligodendrocytes. Microglia and astrocytes are the main key players in the immune response in the central nervous system (Miller and Raison, 2016). Microglia is the resident macrophages of the central nervous system and it adopts different phenotypes in response to inflammatory and injury stimuli (Mondelli et al., 2017). In an activated state, microglia secretes numerous pro- inflammatory cytokines and chemokines, including interleukin (IL) 1, IL-6, IL-12, and tumor necrosis alpha (TNF-α) (Mondelli et al., 2017). Astrocytes are the most numerous glial cells and can be activated by pro-inflammatory cytokines produced by microglia. Astrocytes have several active roles in the brain, including phagocytic properties and secretion of pro-inflammatory cytokines (IL-6, TNF-α) (Rajkowska and Stockmeier, 2013). Oligodendroglia is a glial cell which derives from

oligodendrocytes progenitor cells and plays a key role in myelination (Mechawar and Savitz, 2016). It can produce cytokines (IL-1) and chemokines (monocytes chemoattractant protein 1) post injury (Mechawar and Savitz, 2016).

Previous research has implemented different methodological approaches to address the question on the presence of neuroinflammation in MDD. Most studies investigating brain immune cells have focused on post-mortem brain tissue. However, more recently, in order to investigate microglia activation in humans in vivo, an increasing number of studies have used brain PET scans and measured expression of the translocator protein (TSPO). Increased TSPO expression was initially proposed as an indirect measure of microglia activation; however, this view has been challenged by a recent study suggesting that increased TSPO expression in humans may reflect local myeloid cell proliferation or an increased monocyte recruitment rather than activation of microglia (Owen, et al. 2017).

A number of previous meta-analyses (Wang and Miller, 2018) and reviews (Czeh and Nagy, 2018; Mechawar and Savitz, 2016; Rajkowska and Stockmeier, 2013) have been published in the last few years in this field by focussing on specific aspects or areas of neuroinflammation. A recent meta-analysis focused specifically on CSF cytokines in patients with MDD, schizophrenia and bipolar disorder, and found increased CSF levels of IL-6 and IL-8 in these patients (Wang and Miller, 2018); however, this systematic review and meta-analysis did not include two previous studies, which focused exclusively on major depression (Hestad et al., 2016; Stubner et al., 1999). Another recent article reviewed evidence on glial markers from post-mortem studies, highlighting the role of microglial activation and reduction in astrocytes function in patients with MDD; however, this was not

a systematic review and did not present the large amount of inconclusive post-mortem studies on glial markers in patients with MDD and bipolar disorder (Czeh and Nagy, 2018).

The aim of this paper is to systematically review all studies focusing on markers of central inflammation *in vivo* (CSF and PET markers of inflammation) and in post-mortem in patients with MDD compared with controls and to discuss how the findings for each component (cytokines, microglia, astrocytes, oligodendrocytes) may integrate with each other. We additionally used a meta-analytical approach to summarise data when the quality of studies would allow for such approach. A secondary aim of the paper was to review data on central inflammation more specifically in relation to suicidality in patients with MDD.

2. Methods

2.1 Search strategy

This study followed the PRISMA guidelines for conducting and reporting systematic reviews (Panic et al., 2013). The original publications were identified by searching Pub Med electronic database and by scanning reference lists until December 2018. One reviewer (ED) screened the titles and the abstracts for eligibility. Two reviewers (ED and MV) assessed all publications of potential relevance for inclusion.

We searched the English literature after search words: [“inflammation” OR “cytokines” OR “cerebrospinal fluid cytokines” OR “TSPO” OR “PET microglia”] AND [“depression” OR “major depression”]. For post-mortem studies we searched after the words [“inflammation” OR “microglia” OR “astrocytes” OR “cytokines”] AND “major depressive disorder” OR “depression”] AND “post-mortem” (Figure 1).

2.2 Study selection and data extraction

Inclusion criteria were: (a) patients with unipolar major depressive disorder; (b) comparison with controls; either (c) PET imaging of microglia and/or CSF cytokines and chemokines in subjects with depression as compared with subjects without depression; or (d) cell type specific markers for astrocytes, microglia and cytokines in post-mortem brains of MDD.

Exclusion criteria were: (a) depressive symptoms or MDD in other major psychiatric disorders as bipolar disorder, schizophrenia, eating disorders, mild and major neurocognitive disorders; (b) assessment of only plasma or serum cytokines and chemokines and no assessment of central inflammatory marker; (c) assessment of others inflammatory biomarkers in the CSF such as substance P or corticotrophin-releasing factor; (d) use of non-cell specific markers for astrocytes and microglia in post-mortem studies.

We retrieved 8781 studies in PubMed and Medline databases assessing *in-vivo* and post-mortem markers of inflammation in patients with depression. After removing reviews articles, articles written in other languages than English and studies involving animals, we included 360 studies for revision. Sixty-nine original publications met all the inclusion criteria (Figure 1). The main characteristics and findings of the studies are presented in Tables 2, 3, 4, 5, and Supplementary Tables 1, 3 and 4.

From the included studies we extracted information on: (a) the population (number of participants in the study, age, number of patients with MDD, severity of depression (mean (SD) of the score on depression scales); (b) type of the biomarker of inflammation (cytokines and chemokines, PET microglia); (c) type of the biomarker of inflammation in post-mortem studies (cell specific markers for microglia, astrocytes and oligodendrocytes, levels of

cytokines and chemokines); (d) outcome levels of biomarkers in patients with MDD and controls (mean and standard deviations).

2.3 Statistical analysis

A meta-analysis approach was used only for *in vivo* studies of CSF and PET markers of inflammation in patients with MDD, as post-mortem studies were too varied to allow using this approach. From each article included in the meta-analysis we extracted data on sample size, mean and standard deviation, number of patients with MDD and controls. When needed we estimated mean ± standard deviation (S.D.) from median/range or interquartile range/standard error of the mean using formulas previously described (Hozo et al., 2005). We calculated standardised mean difference (SMD) as a measure of effect size and the 95% confidence intervals (95% CIs). *P*-values<0.05 were considered statistically significant. The heterogeneity in the analysis was assessed with χ^2-test (the heterogeneity in effect size estimates) and I^2 –index (estimated percentage of variation in effect size attributable to heterogeneity). The pooled analysis was considered significantly heterogeneous if the *p*-value in the χ^2-test was below 0.05 and I^2 –index was more than 50%. We carried out a sensitivity analysis to examine the impact of individual studies on the heterogeneity by excluding one study at a time and repeated the meta-analysis procedure. The statistical analyses were performed with the software STATA 15 (StataCorp LP).

3. Results

3.1 CSF or PET biomarkers of inflammation in patients with depression

3.1.1. CSF cytokines and chemokines in patients with depression

We included 12 studies which investigated cytokines, chemokines and complement C5 in CSF of MDD patients (Blasko et al., 2006; Boufidou et al., 2009; Carpenter et al., 2004; Hestad et al., 2016; Ishii et al., 2018; Kern et al., 2014; Levine et al., 1999; Lindqvist et al., 2009; Martinez et al., 2012; Palhagen et al., 2010; Sasayama et al., 2013; Stubner et al., 1999).

CSF levels of IL-6 were measured in 9 studies. Three studies reported increased levels of IL-6 in patients with MDD compared with controls (Lindqvist et al., 2009; Martinez et al., 2012; Sasayama et al., 2013) , while 2 studies reported decreased levels of CSF IL-6 in patients with MDD compared with controls (Levine et al., 1999; Stubner et al., 1999). Four studies found similar levels of CSF IL-6 between patients with MDD and controls (Carpenter et al., 2004; Hestad et al., 2016; Kern et al., 2014; Palhagen et al., 2010). Five studies measured CSF levels of TNF-α and all reported similar CSF levels of TNF-α between MDD and controls (Blasko et al., 2006; Hestad et al., 2016; Levine et al., 1999; Lindqvist et al., 2009; Martinez et al., 2012). Three studies measured CSF levels of IL-8 (Hestad et al., 2016; Kern et al., 2014; Lindqvist et al., 2009), one study reported increased CSF levels of IL-8 (Kern et al., 2014) and two studies reported similar levels between MDD and controls (Hestad et al., 2016; Lindqvist et al., 2009). Three studies measured CSF levels of IL-1β (Hestad et al., 2016; Levine et al., 1999; Lindqvist et al., 2009). One study found increased CSF levels of IL-1β in patients with MDD compared with controls (Levine et al., 1999), while two others reported similar levels between MDD and controls (Hestad et al., 2016; Lindqvist et al., 2009).

Most of the studies included small samples and reported conflicting results on the CSF levels of IL-6, TNF-α, IL-8 and IL-1β in patients with MDD. We employed a meta-analysis method to

estimate the difference between patients with MDD and controls. CSF levels of IL-6, TNF-α and IL-8 were significantly increased in patients with MDD compared with controls (CSF IL-6: SMD 0.37, 95%CI: 0.17- 0.57, z=3.57, p<0.001, χ^2= 68.66, p<0.0001, I^2=88.3%; CSF TNF-α: SMD 0.58, 95%CI: 0.30- 0.45, z=3.59, p<0.0001, χ^2= 61.20, p<0.0001, I^2=95.1%; CSF IL-8: SMD 0.82, 95%CI: 0.52- 1.13, z=5.28, p<0.0001, χ^2= 13.62, p=0.001, I^2=85.3%) (Figure 2). Heterogeneity was very high across the studies. In a sensitivity analysis for CSF IL-6 heterogeneity was no longer significant after excluding Lindqvist et al(Lindqvist et al., 2009), Levine et al (Levine et al., 1999) and Stubner et al (Stubner et al., 1999) (SMD 0.40, 95%CI: 0.17, 0.63, z=3.4, p=0.001, χ^2 = 4.3, p=0.5, I^2=0%). In a sensitivity analysis CSF levels of TNFα were similar between patients with MDD and controls after excluding Lindqvist *et al* (Lindqvist et al., 2009) (SMD -0.07, 95%CI: -0.43, 0.30, z=0.4, p=0.7, χ^2= 0.80, p=0.7, I^2=0%). Table 1 illustrates the results of the sensitivity analysis performed for CSF levels of IL-8 and IL-1β.

A longitudinal study of pregnant women by Boufidou and colleagues focussing on women at risk of developing postpartum depression was included for the purposes of the review but not for the meta-analysis. The authors found that high CSF levels of IL-6 and TNF-α at the time of delivery were positively associated with the occurrence of depressive symptoms postpartum at 4 days and 6 weeks after delivery (Boufidou et al., 2009) .

Two studies reported on CSF levels of chemokines. Blasko and colleagues found similar CSF levels of monocyte chemoattactant protein 1 (MCP-1) and macrophage inflammatory protein 1 alpha (MIP-1α) in MDD compared with controls (Blasko et al., 2006). While Janelidze and colleagues found that patients with MDD and suicide attempt had lower CSF levels of chemokines monocyte chemotactic protein 4 and thymus and activation-regulated

chemokine compared with controls (Janelidze et al., 2013).

3.1.2. PET translocator protein (TSPO) expression in patients with depression

This is the first meta-analysis published on PET (translocator protein) TSPO studies in patients with MDD. We included 6 studies assessing the brain TSPO expression on 147 patients with MDD and 106 controls (Hannestad et al., 2013; Holmes et al., 2018; Li et al., 2018; Richards et al., 2018; Setiawan et al., 2018; Su et al., 2016). First (Holmes et al., 2018; Su et al., 2016) and second (Hannestad et al., 2013; Li et al., 2018; Richards et al., 2018; Setiawan et al., 2018) generation TSPO PET tracers were used. Out of the 6 studies, 5 studies found elevated TSPO in different brain regions of patients with MDD compared with controls (Holmes et al., 2018; Li et al., 2018; Richards et al., 2018; Setiawan et al., 2018; Su et al., 2016), while one study found similar TSPO levels between MDD and controls (Hannestad et al., 2013).

We employed a meta-analysis to explore the brain regions where the TSPO expression is more pronounced. TSPO was elevated in patients with MDD compared with controls in the anterior cingulate cortex (SMD0.71, 95%CI 0.40-1.03) (Holmes et al., 2018; Richards et al., 2018; Setiawan et al., 2018; Su et al., 2016), temporal lobe, (SMD 0.51, 95%CI: 0.18- 0.84) (Hannestad et al., 2013; Li et al., 2018; Setiawan et al., 2018), frontal lobe (Hannestad et al., 2013; Li et al., 2018), prefrontal cortex (Holmes et al., 2018; Setiawan et al., 2018), insula (Holmes et al., 2018; Setiawan et al., 2018), and hippocampus (Li et al., 2018; Setiawan et al., 2018). The levels of translocator protein were similar between patients with MDD and controls in the occipital cortex (Hannestad et al., 2013; Setiawan et al., 2018), parietal cortex (Hannestad et al., 2013; Setiawan et al., 2018) and thalamus (Hannestad et al., 2013; Setiawan et al., 2018) (See Figure 3, Table 3, Supplementary Table 2).

3.1.3. Correlations between central and peripheral markers of inflammation

Out of 22 studies on CSF and PET-TSPO, 9 studies conducted correlation analyses between markers of central inflammation and peripheral inflammation (Bay-Richter et al., 2015; Hannestad et al., 2013; Hestad et al., 2016; Holmes et al., 2018; Isung et al., 2012; Levine et al., 1999; Lindqvist et al., 2009; Sasayama et al., 2013; Setiawan et al., 2015). Seven studies found no correlation between markers of central inflammation (CSF cytokines or PET TSPO) and peripheral inflammation (Bay-Richter et al., 2015; Hannestad et al., 2013; Holmes et al., 2018; Isung et al., 2012; Lindqvist et al., 2009; Sasayama et al., 2013; Setiawan et al., 2015). Hestad and colleagues found a moderate correlation between serum and CSF levels of eotaxine, interferon-inducible protein 10 and macrophage inflammatory protein 1 beta in patients with MDD (Hestad et al., 2016). Levine and colleagues found a correlation between CSF levels of IL-1β and serum levels of TNF (Levine et al., 1999) .

3.2 Markers of inflammation in post-mortem studies of patients with depression

As mentioned above, after careful consideration a meta-analysis was not possible for the post-mortem studies as different cell-specific markers of glial cells are measured, often repeatedly in the same small samples of post-mortem brains cohorts. Moreover, different cellular and molecular inflammatory markers were measured in different brain regions, using a broad range of methods and techniques.

3.2.1 Cytokines, chemokines and other inflammatory markers in post-mortem studies

Ten studies measured cytokines (Clark et al., 2016; Dean et al., 2013, 2010; Hoyo-Becerra et al., 2013; Pandey et al., 2019, 2012; Pantazatos et al., 2017; Tonelli et al., 2008; Wang et al., 2018) and chemokines (Clark et al., 2016; Torres-Platas et al., 2014) expression in postmortem brains of MDD (supplementary Table 3). The presence of cytokines and chemokines in

postmortem MDD brains is debatable, with some studies reporting increased expression of TNFα and monocyte chemoattractant protein-1 (MCP-1) (Dean et al., 2010 Wang et al., 2018; Torres-Platas et al., 2014), other studies reporting reduced expression of TNFα, IL-8, MCP-1 and macrophage inflammatory protein 1 beta (MIP-1β) (Clark et al., 2016; Pantazatos et al., 2017), and other authors finding similar levels of TNFα, and IL-6 between subjects with MDD and controls (Dean et al., 2013; Tonelli et al., 2008). Although IL-6 mRNA was no different between depressed and controls subjects, IL-6 mRNA has been reported to be increased in suicide victims (Hoyo-Becerra et al., 2013; Pandey et al., 2012). When reviewing studies investigating other inflammation-related markers, Clark et al. found lower quinolinic levels and lower kynurenine: tryptophan ratio in brains of patients with MDD (Clark et al., 2016).

3.2.2 Microglia in post-mortem brains of patients with depression

We included 8 studies which investigated microglial markers in post-mortem brains of patients with MDD (Brisch et al., 2017; Busse et al., 2015; Clark et al., 2016; Foster et al., 2006; Steiner et al., 2011, 2008; Torres-Platas et al., 2014; Wesseling et al., 2014)(Table 4).

Of the 8 studies, 4 did not detect any MDD related changes (Brisch et al., 2017) (Torres-Platas et al., 2014) (Steiner et al., 2008) (Foster et al., 2006). The other four reported conflicting findings. Clark et al reported an increase in the proportion of IBA1-positive amoebian (active) microglia in the ventrolateral prefrontal cortex of patients with MDD compared with controls and similar density of hypertrophic (non-active) microglia (Clark et al., 2016). Wesseling et al reported lower levels of coronin1A, a marker of microglia (Wesseling et al., 2014) in MDD compared with controls. The other 2 studies focussed on quinolinic immunoreactive microglia, with Busse et al showing a reduction in the

hippocampal cornu ammonis 1 (CA1) (Busse et al., 2015), while Steiner et al reporting an increase in the subgenual ACC and anterior midcingulate cortex, notably from post-mortem brain from the same biobank (Steiner et al., 2011).

Of note only 4 out of 8 studies investigated microglia morphology between MDD and controls (Clark et al. 2016, Steiner et al 2011, Torres-Platas et al 2014, Brisch et al., 2017). Of these 4 studies, 3 reported increase in density of activated microglia according to morphology (Clark et al. 2016, Steiner et al 2011, Torres-Platas et al 2014), while one reported no differences between groups when looking at microglia morphology (Brisch et al., 2017).

Cause of death was suicide for most of the subjects with MDD. Two studies included only MDD subjects who died through suicide (Busse et al., 2015). Increased density of microglia (microgliosis) was reported in suicide victims irrespective of psychiatric diagnosis (Steiner et al., 2011).

3.2.3 Astrocytes in post-mortem brains of patients with depression

We included 24 studies which assessed astrocytes in postmortem brains of patients with MDD (Altshuler et al., 2010; Barley et al., 2009; Bernard et al., 2011; Chandley et al., 2013; Cobb et al., 2016; Damadzic et al., 2001; Davis et al., 2002; Fatemi et al., 2004; Gos et al., 2013; Miguel-Hidalgo et al., 2014, 2011, 2010, 2000, 2017; Rajkowska et al., 2018; Ramaker et al., 2017; Toro et al., 2006; Torres-Platas et al., 2016, 2011, Webster et al., 2005, 2001; Wesseling et al., 2014; Williams et al., 2014; Zhao et al., 2016) (Table 5). Cause of death was suicide for most of the subjects with MDD included. Two studies included only MDD suicide victims (Torres-Platas et al., 2016, 2011), while one study excluded MDD suicide victims(Davis et al.,

2002). Of the 24 studies, 13 studies found a decrease in the astrocytes specific markers, 3 reported an increase, whereas 11 studies found similar levels of astrocytes specific markers between patients with MDD and controls. The markers used to investigate astrocytes varied across the studies, with 20 studies focusing on glial fibrillary acidic protein (GFAP) expression or immunoreactivity distribution and 9 studies investigating other markers including S100 calcium binding protein B (S100B), glutamate transporters genes or performing morphometric analyses. Reactive astrocytes have an increased expression of glial fibrillary acidic protein (GFAP), which in postmortem studies is used as astrocytes specific marker (Rajkowska and Stockmeier, 2013).

When focusing only on the immunohistochemical studies investigating GFAP immunoreactivity between patients with MDD and controls, four studies found a reduction in GFAP immunoreactive astrocytes in MDD compared with controls in the basolateral nucleus of the amygdala (Altshuler et al., 2010), orbitofrontal cortex (Miguel-Hidalgo et al., 2010), locus coeruleus (Chandley et al., 2013) and white matter in ventral prefrontal cortex (Rajkowska et al., 2018); six studies found similar GFAP immunoreactive astrocytes between patients with MDD and controls, in the hippocampus (Cobb et al., 2016), dorsolateral prefrontal cortex (Miguel-Hidalgo et al., 2000), orbitofrontal cortex (Toro et al., 2006), entorhinal cortex (Damadzic et al., 2001), substantia nigra (Williams et al., 2014), and anterior cingulate cortex (Davis et al., 2002); and only one study showed higher GFAP immunoreactivity in dorsolateral prefrontal cortex in brains of elderly patients with MDD (Davis et al., 2002). In contrast, another study reported a decrease in phosphorylated GFAP-positive cells in contact with the blood vessels of the dorsolateral prefrontal cortex in MDD (Webster et al., 2001).

Lower mRNA or protein levels of GFAP in MDD compared with controls were found in mediodorsal thalamus (Torres-Platas et al., 2016), caudate nucleus (Torres-Platas et al., 2016), locus coeruleus (Bernard et al., 2011; Chandley et al., 2013), orbitofrontal cortex (Miguel-Hidalgo et al., 2017), lateral cerebellum (Fatemi et al., 2004), and white matter in ventral prefrontal cortex (Rajkowska et al., 2018). Only one study reported higher GFAP mRNA in thalamus (anteroventral nucleus, mediodorsally nucleus), intern capsule and putamen in MDD (Barley et al., 2009). Two studies found similar mRNA or protein levels of GFAP between MDD and controls in cerebellar cortex, primary motor cortex (Brodmann's area-BA- 4), primary visual cortex (BA 17) (Torres-Platas et al., 2016), and in anterior cingulate cortex (Webster et al., 2005). The results regarding other astrocytic markers are summarized in Table 5.

3.2.4 Oligodendrocytes in post-mortem brains of patients with depression

We included 12 studies which measured oligodendrocytes in post-mortem MDD brains (Aston et al., 2005; Barley et al., 2009; Gos et al., 2013; Hayashi et al., 2011; Honer et al., 1999; Lutz et al., 2017; Miguel-Hidalgo et al., 2017; Rajkowska et al., 2015; Tanti et al., 2018; Uranova et al., 2004; Vostrikov et al., 2007; Williams et al., 2014). Cause of death was suicide for most of the MDD subjects. Two studies included only MDD suicide victims (Lutz et al., 2017; Tanti et al., 2018)(Supplementary table 4).

Six studies measured markers of oligodendrocytes in the prefrontal cortex. Four out of six reported a decrease in oligodendrocytes in this brain region (Hayashi et al., 2011; Miguel-Hidalgo et al., 2017; Uranova et al., 2004; Vostrikov et al., 2007). Uranova et al, Vostrikov et al and Hayashi et al reported in the same cohort of MDD brains from Stanley Foundation Neuropathology Consortium a reduction in the whole population of oligodendrocytes in the

gray matter of the prefrontal cortex (BA 9) layer VI (Uranova et al., 2004) , and layer III (Vostrikov et al., 2007), and in the frontopolar prefrontal cortex (BA 10) (Hayashi et al., 2011) .

Using immunohistochemical analysis for the whole population of oligodendrocytes, 5 studies reported a similar density of oligodendrocytes in post-mortem brains of patients with MDD and those of controls in the white matter of ventromedial (Tanti et al., 2018), ventral prefrontal cortex (Rajkowska et al., 2015), in the gray matter of substantia nigra (Williams et al., 2014), hippocampus (Gos et al., 2013) and anterior cingulate cortex (Lutz et al., 2017). Rajkowska et al found a decreased soma size of oligodendrocytes in the gyral white matter of the ventral prefrontal cortex in MDD, but a similar soma size of oligodendrocytes in the deep white matter of the ventral prefrontal cortex between MDD and controls (Rajkowska et al., 2015). Using PCR, Aston et al found decreased transcription factors OLIG2 and SOX 10 mRNA in temporal lobe of MDD brains compared with controls (Aston et al., 2005), while Barley et al found similar expression of Sox10 and OLIG 2 mRNA in the thalamus (anteroventral nucleus, mediodorsal nucleus), internal capsule and putamen of MDD compared with control brains (Barley et al., 2009).

Tanti el al and Lutz et al reported a reduction in whole population of oligodendrocytes in the white matter of the ventromedial prefrontal cortex and of the anterior cingulate cortex of MDD suicide victims with childhood abuse compared with MDD suicide victims without childhood abuse and normal controls (Lutz et al., 2017; Tanti et al., 2018).

3.3 Markers of central inflammation and suicidal behaviour in MDD

3.3.1 CSF Cytokines in subjects with suicidal behaviour

We included 5 studies which measured the CSF levels of cytokines and chemokines in patients with suicide attempts regardless of their diagnosis. Suicide attempters regardless of the neuropsychiatric disorder had higher CSF levels of IL-6 (Lindqvist et al., 2009) and quinolinic acid (Bay-Richter et al., 2015; Erhardt et al., 2013), but lower CSF levels of kynurenic acid, endotaxin1, macrophage inflammatory protein 1β, monocyte chemoattractant protein-1, monocyte chemotactic protein 4 and thymus and activation-regulated chemokine than controls (Bay-Richter et al., 2015; Janelidze et al., 2013). Erhardt et al (Erhardt et al., 2013) and Bay-Richter et al (Bay-Richter et al., 2015) reported in two studies from the same cohort that CSF levels of quinolinic acid decreased at 6 months follow up (Erhardt et al., 2013), but remain higher at almost 2 years after a suicide attempt (Bay-Richter et al., 2015). In another cohort of patients with suicide attempts Isung et al found lower CSF levels of IL-8 in patients with a suicide attempt compared with controls, but the authors reported similar CSF levels of IL-6 between suicide attempters and controls (Isung et al., 2012).

3.3.2 Markers of central inflammation between depressed subjects with suicidal behaviour and depressed subjects without suicidal behaviour

In this review we also try to highlight CSF, PET and post-mortem studies, which compared different inflammatory markers between patients with MDD with suicidal behaviour and MDD without suicidal behaviour.

Martinez et al reported a positive correlation between levels of CSF IL-6 and IL-1 and suicidal ideation (Martinez et al., 2012). We found one PET study, which reported microglia

activation only among the 9 MDD patients with suicidal thoughts compared with 5 MDD patients without suicidal thoughts and controls (Holmes et al., 2018).

In post-mortem studies suicide was main cause of death for individuals with MDD. In a post-mortem study Wang et al (Wang et al., 2018) found similarly increased levels of TNF-α mRNA, and Pantazatos et al (Pantazatos et al., 2017) found similarly lower IL-8 and chemokine macrophage inflammatory protein 1 beta in MDD suicide victims compared with MDD non-suicide victims.

Pandey et al (Pandey et al., 2019, 2014) found similar levels of toll like receptor 1, 2, 3, 4 mRNA in MDD suicide victims and MDD no suicide victims, but increased levels of protein toll like receptor 3, 4 and 6 in MDD suicide victims compared with MDD non-suicide victims (Pandey et al., 2019).

Zhao et al found reduced levels of astrocytes specific glutamate reuptake transporter mRNA in MDD suicide victims compared with MDD non-suicide victims (Zhao et al., 2016). Miguel-Hidalgo et al found similarly low levels of astrocytes connexin 43 protein in MDD suicide victims and MDD non-suicide victims compared with controls (Miguel-Hidalgo et al., 2014). Tanti el al and Lutz et al reported a similar density of oligodendrocytes in MDD suicide victims compared with MDD non-suicide victims (Lutz et al., 2017; Tanti et al., 2018).

4. Discussion

Our systematic review and meta-analysis support the presence of increased neuroinflammation in patients with MDD as shown by increased pro-inflammatory cytokines in CSF. At cellular level, our paper suggests the presence of microglia activation but not necessarily an increased density of microglia, as indicated by the post-mortem

studies showing an increased in primed and activated microglia. Density of astrocytes and oligodendrocytes in brains of patients with MDD appears mainly reduced or similar to that of controls.

This paper summarizes the overall evidence of different markers of neuroinflammation in patients with MDD, rather than focussing on a single or a couple of markers. This is particularly important if we want to better understand the communication between immune and central nervous system, given the role of the cross-talk between microglia, astrocytes and oligodendrocytes plays in maintaining the brain homeostasis.

Our review shows that patients with MDD have increased levels of CSF cytokines such as IL-6 and IL-8 and an increased expression of TNF-α mRNA (Wang et al., 2018), monocytes chemoattractant protein 1 mRNA (Torres-Platas et al., 2014) and toll like receptor 3 and 4 in post-mortem brains (Pandey et al., 2014). Toll like receptor 3 and 4 mediate the activation of microglia and increase the production of proinflammatory cytokines in the dorsolateral prefrontal cortex (Facci et al., 2014; Pandey et al., 2014). PET studies show an elevated TSPO in specific brain regions in patients with MDD, including the anterior cingulate cortex, frontal cortex, temporal cortex, hippocampus and insula. The increased expression of TSPO from brain PET studies in MDD is difficult to interpret given that the notion that TSPO expression is a marker of microglia activation has been recently challenged by an in vitro study (Owen, et al. 2017). The recent study suggests that increased TSPO expression in humans may indicate instead an increased monocyte recruitment. This appears possibly in agreement with post-mortem studies. Indeed, Torres Platas et al (2014) reported a higher proportion of blood vessels surrounded by a high density of macrophages in MDD suicide victims than in controls, suggesting an increased recruitment of peripheral monocytes in

suicidal patients (Torres-Platas et al., 2014). These findings support the hypothesis that cytokines and chemokines play a key role in recruiting peripheral monocytes and activating microglia without necessary the occurrence of microgliosis. Although post-mortem studies found similar density of microglia in patients with MDD and in controls, Torres-Platas et al found an increased ratio of primed over ramified (‘‘resting’’) microglia in the anterior cingulate cortex of MDD suicide victims compared with brains from controls (Torres-Platas et al., 2014). Activated microglia release pro-inflammatory cytokines (such as IL-6 (Wang and Miller, 2018) and TNF-α (Wang et al., 2018)). Cytokines administration has been shown to induce activation of the hypothalamic–pituitary–adrenal (HPA) axis and peripheral glucocorticoid secretion (Felger and Lotrich, 2013). In turn, glucocorticoids modulate the microglial activation and the activity of the HPA axis (Walker and Spencer, 2018). Most of the studies on CSF and PET could not find a correlation between peripheral and central cytokines. These findings may question the hypothesis that central inflammation derives from an increased peripheral inflammation in major depressive disorders (Miller and Raison, 2016). However, the lack of correlation between peripheral and central cytokines may also be due to other possible moderating factors such as the permeability of the blood brain barrier (Miller and Raison, 2016).

The implication of astrocytes and oligodendrocytes in the immune response is more debatable. Astrocytes play a key role in maintaining the neurotransmitters homeostasis (glutamate and GABA), water transport homeostasis, ion homeostasis, metabolic support, synaptogenesis and synaptic plasticity, maintaining the integrity of the blood brain barrier (Verkhratsky and Nedergaard, 2018). The post-mortem studies show that several specific markers for astrocytes, such as GFAP, gap junction proteins (conexinne 43, water channel

aquaporine 4, calcium binding protein S100B, the glutamate transporters (EAAT1, EAAT2 or SLC1A3 and SLC1A2) and glutamine synthetase are reduced in patients with MDD)(Bernard et al., 2011; Chandley et al., 2013; Miguel-Hidalgo et al., 2011). The reduction in the astrocytes specific markers was found in brain areas that are well known to be involved in depressed mood and anhedonia such as the prefrontal cortex (Miguel-Hidalgo et al., 2017, 2011, 2010; Webster et al., 2001), anterior cingulate cortex (Torres-Platas et al., 2011; Wesseling et al., 2014), amygdala (Altshuler et al., 2010) and locus coeruleus (Bernard et al., 2011; Chandley et al., 2013). The reduction in the astrocytes markers may reflect impairment of their function, including possibly an effect on the integrity of the blood brain barrier, particularly the S100B (Gos et al., 2013). Some studies, which found a decreased in neurotrophic factors in patients with MDD, argue that in patients with MDD there is primarily an impairment in synaptic plasticity and neuroplasticity (Martinez et al., 2012)(Rajkowska and Stockmeier, 2013).

Post-mortem morphometry studies found no difference in the astrocytes soma between MDD and controls, which suggest that there is no atrophy or degeneration of the astrocytes in gray and white matter (Rajkowska et al., 2018; Torres-Platas et al., 2011). Post-mortem studies which measured the glutamate transporters in astrocytes found a reduction in the SCL1 gene expression and its protein the glutamate transporter EAAT1, suggesting an impairment of the glutamate reuptake from the synaptic cleft (Miller and Raison, 2016). Additionally, the GAP junction between astrocytes and astrocytes and between astrocytes and neurons may be affected and this would lead to an impairment in the ion homeostasis and synaptic circuit (Rajkowska and Stockmeier, 2013; Verkhratsky et al., 2014).

The concomitant activation of microglia and reduced function of astrocytes could also have downstream effects on the kynurenine pathway (Dantzer et al., 2011). Cytokines may activate the indolamine 2,3-dioxygenase (IDO) an enzyme expressed in microglia and astrocytes. IDO is catabolising the amino acid tryptophan, essential precursor of serotonin neurotransmitter into different metabolic products. Two of the end products of the kynurenine pathway are the quinolinic (QUIN) and kynurenic (KYNA) acid (Dantzer et al., 2011). Microglia expresses the enzyme kynurenine-3-monooxygenase which is essential to produce QUIN, while astrocytes express the enzyme kynurenine aminotransferase essential to produce KYNA. QUIN is regarded as a neurotoxic end product of the kynurenic pathway, while KYNA is neuroprotective (Borsini et al., 2015; Miller and Raison, 2016). Therefore, an unbalance between microglia and astrocytes activation may influence production of QUIN and KYNA. These two metabolites also interact with glutamate neurotransmitter system. QUIN has been shown to activate the *N*-methyl-D-aspartate receptor (NMDA) and to increase the glutamate in the synaptic cleft through increase glutamate release and decrease the glutamate reuptake by the astrocytes (Dantzer et al., 2011). Some post-mortem studies found increased density of QUIN-positive microglia cells in the subgenual anterior cingulate cortex and the anterior midcingulate cortex of MDD patients, and a decreased re-uptake of glutamate from the synaptic cleft (Bernard et al., 2011; Chandley et al., 2013; Steiner et al., 2011). Furthermore, an increased level of cytokines and impairment in astrocytes function may lead to an impairment of the myelination and reduced oligodendrocytes density (Barnett and Linington, 2013; Rajkowska et al., 2018). In agreement with this possible effect on oligodendrocytes density, studies included in this review show a reduction in oligodendrocytes markers in the prefrontal cortex, but no MDD changes in other brain regions of MDD brains. This is in line with diffusion tensor imaging

studies which reported reduced fronto-subcortical connectivity in patients with MDD, disruptions which occur in early stages of the disease (Liao et al., 2013; Ma et al., 2007).

4.1 Methodological considerations

One limitation in this review is the increased heterogeneity across studies in study design, methodology used to measure inflammatory markers, and sample selection. For example, CSF and PET studies included patients with different degrees of severity of MDD (current or remitted depression). Some CSF and PET tried to address the role of antidepressants in inflammation including patients with MDD who were drug-free for several weeks and months before the assessment (Martinez et al., 2012; Richards et al., 2018; Setiawan et al., 2018). However, almost all post-mortem studies included patients with MDD who were exposed to several psychotropic medications (antidepressants, sedative hypnotics and antipsychotics) before death. There is also heterogeneity due to specific methodology and outcome measures. A previous meta-analysis found elevated TSPO binding in patient with schizophrenia when the outcome was TSPO- Binding Potential (BP_{ND}), but not when the outcome was TSPO- Volume of Distribution (V_T) (Marques et al., 2018). In our meta-analysis four out of six studies used TSPO- V_T, while two other studies used TSPO-BP_{ND}. Microglia activation appears mainly supported by post-mortem studies looking specifically at microglia morphology and further studies would need to be conducted to further confirm this finding.

Suicidal behaviour is part of clinical assessment of MDD; therefore, it was difficult to include only studies assessing inflammatory markers in MDD without suicidal behaviour. Few in vivo

CSF and PET studies reported on the degree of suicidal behaviour of the patients with MDD. Most of the post-mortem studies were conducted in a mixed population of MDD suicide and non-suicide victims, and the cohorts are not always well characterized. In addition, most of the post-mortem studies measured the glial cells and cytokines in different brain regions. Controls where recruited from different clinics, sometimes from neurological department: in post-mortem studies the main cause of death for controls was cardiovascular diseases which are also associated with altered inflammatory processes (Ruparelia et al., 2017).

4.2 Conclusions

Our paper suggests the presence of neuroinflammation in patients with MDD which is mainly characterized by increased levels of pro-inflammatory cytokines in CSF and increased activation of microglia without microgliosis and decreased density of astrocytes and prefrontal cortex oligodendrocytes. This suggests that specific changes in the cross-talk of the different glial cells may contribute to a disruption in the communication between the immune and central nervous system and downstream alterations of the kynurenine pathway and glutamatergic function in patients with MDD.

Legend to Figures

Figure 1: Prisma diagram of the literature search.

Figure 2: Forest plot presenting increased CSF levels of IL-6 in patients with MDD compared with healthy controls.

Figure 3: Meta-analysis of PET TSPO expression data for specific brain regions in patients with MDD vs healthy controls.

Figure 4: Proposed model of disruption in the communication between brain immune cells in patients with MDD. The review highlights the co-occurrence of a reduction in number of astrocytes and of microglia activation that can affect dysregulation of the kynurenine pathway and glutamatergic function. The reduction of astrocytes could also contribute to reduction in oligodendrocytes and to a reduction integrity of blood brain barrier and therefore increased recruitment of monocytes. Both monocyte infiltration and microglia activation could partly contribute to increased levels of cytokines in CSF and brain parenchyma. CSF: cerebrospinal fluid; BBB: blood brain barrier.

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